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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,718	05/08/2002	Audrey Goddard	P3230R1C001-168	8618

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,718	EATON ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The Amendment and Declarations under 37 CFR § 1.132, all submitted 29 October 2004, have been entered. Claim 15 is cancelled.

In view of the papers filed 29 October 2004, the inventorship in this nonprovisional application has been changed by the deletion of: Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen and Colin K. Watanabe.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Claims 1-14 and 16-20 are under examination in the Instant Application.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

Withdrawn Objections And/or Rejections

URL's

The objection to the Specification because it contained browser-executable code, is *withdrawn.* Applicants amended the Specification to remove all URL's (29 October 2004).

35 USC § 112, first paragraph – Deposit Rules

The rejection of Claims 1-6, 8-10 and 11-13 under 35 U.S.C. § 112, first paragraph, for not complying with the enablement requirement, is *withdrawn in part.* Specifically, Applicants amended the Specification to insert language guaranteeing unrestricted availability of the deposited nucleic acid molecules (clone DNA66658-1584), and pointed out that the instant Specification lists the ATCC address. Please see sections on 35 USC §101 and §112, 1st paragraph (below) for maintained portions of the rejection.

35 U.S.C. § 112, first paragraph-, Written Description.

The rejection of Claims 1-6 and 8-20 under 35 U.S.C. § 112, first paragraph, Written Description, is *withdrawn in part.* Applicants amended claims to insert language pertaining to functional regions of SEQ ID NO: 94 that had not been identified (i.e, "extracellular domains"), but have not removed references to amino acids having 80-99% sequence identity to the claimed PRO1328 polypeptide (see below).

35 USC § 112, second paragraph

The rejection of Claims 1-6, 9, 10 and 14 under 35 U.S.C. 112, second paragraph, for being indefinite is *withdrawn.* Applicants amended current claims to modify phrases pertaining to a peptide "extracellular domain" (29 October 2004).

The rejection of Claim 15 under 35 U.S.C. 112, second paragraph, for being indefinite is *withdrawn.* Applicants amended the claim to insert "stringent" hybridization conditions supported by the Specification as filed (29 October 2004).

Maintained Objections and/or Rejections

Continuity

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119. Applicants have argued that they are entitled to the benefit of Provisional Application 60/100683. However, since the claimed invention does not have Utility, the Provisional patent applications listed in the disclosure, although disclosing the same experimental assays as the instant specification, do not impart Utility to the instant invention. Therefore, the filing date of 8 May 2002 is considered as the priority date.

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 1-14 and 16-20 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pp. 3-10 of the previous Office Action (29 July 2004). Claims 1-14 and 16-20 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (29 July 2004), one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue (29 October 2004, page 11) that the results presented in the instant Specification are enabling for the polynucleotide of SEQ ID NO: 93. They argue that the PRO1328 nucleic acid is a diagnostic marker for normal lung and melanoma tumor, and point to the results of the amplification assay, which showed an amplification of the PRO1328 DNA in normal lung and melanoma tumor.

Applicant's arguments (29 October 2004) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing a very small increase in DNA copy number- by an indefinite amount, but probably about 2 fold- in normal lung and melanoma tumor tissues. However, there is no evidence regarding whether or not PRO1328 mRNA or polypeptide levels are also increased in these tissues. Furthermore, as discussed in the previous Office Action (29 July 2004, page 9), what is often seen is a *lack* of correlation between DNA amplification and increased peptide levels (Pennica, et al, 1998, Proc. Natl. Acad. Sci., 95: 14717-14722). As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Given the small increase in DNA copy number of PRO1328, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small

increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. Further research needs to be done to determine whether the small increase in PRO1328 DNA supports a role for the peptide in any tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
>
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Specification's assertions that the claimed PRO1328 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

The Declaration of Dr. Polakis, filed under 37 CFR 1.132 (29 October 2004), is insufficient to overcome the rejection of Claims 1-14 and 16-20, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action (29 July 2004).

The Declaration of Dr. Ashkenazi, filed under 37 CFR 1.132 (29 October 2004), is insufficient to overcome the rejection of Claims 1-14 and 16-20, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action (29 July 2004).

Likewise, the Declaration of Dr. Grimaldi, filed under 37 CFR 1.132 (29 October 2004),

is insufficient to overcome the rejection of Claims 1-14 and 16-20, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action because:

In the Declaration filed under 37 CFR 1.132 (29 October 2004), staff scientist Ashkenazi claims that the purpose of the experiments that measured increases in gene copy number was to identify tumor cell markers useful for cancer treatment (page 1, Declaration, 29 October 2004) and to identify cancers for which there was an absence of gene product over-expression (page 2).

The Ashkenazi declaration filed under 37 CFR § 1.132 argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, as discussed above, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

Dr. Grimaldi (Declaration filed under 37 CFR § 1.132, 29 October 2004) states that the gene amplification assay was used to differentiate tumor [tissue] from normal (see paragraph 6), and that the levels of gene expression correlate with RNA and with the protein product: "Comparison of gene expression levels in normal versus diseased tissue has important implications both diagnostically and therapeutically. For example, those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed, as evidenced by an increased production of mRNA, the gene product or polypeptide will also be over-expressed.

It is unlikely that one identifies increased mRNA expression without associated increased protein expression. " (paragraph 5). These points have been fully considered but are not found to be persuasive. Firstly, it is important to note that the instant specification provides no information regarding increased protein, DNA or mRNA levels of PRO1328 in tumor samples as contrasted to normal tissue samples: Only gene amplification data were presented and then only in one cancer tissue and one normal tissue. The Declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1328 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1328 nucleic acid was amplified in some normal tissues, and to a minor degree. No mutation or translocation of PRO1328 has been associated with melanoma tissue. It is not known whether PRO1328 is underexpressed in other normal tissues or overexpressed in other cancers, and what the relative levels of expression are. In the absence of any of the above information, all that the Specification does is present evidence that the DNA encoding PRO1328 is amplified in a small number of dissimilar samples, and invite the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al. (1998, PNAS 95: 14717-14722), the issue is simply not predictable, and the specification presents a mere invitation to experiment.

The Polakis Declaration states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in control tissues and that antibodies have been developed that identify and could possibly be used to downregulate the PRO peptides. Dr. Polakis implies that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr Polakis characterizes the instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. It is important to note that the instant specification provides no information regarding decreased mRNA levels of PRO1328 in tumor samples as contrasted to normal tissue samples: Only gene amplification data were presented. Therefore, the declaration is insufficient to overcome the rejection of Claims 1-14 and 16-20 based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels.

Furthermore, the Declarations do not provide data such that the examiner can independently draw conclusions. Only Doctors Grimaldi, Polakis and Ashkenazi's conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA Levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples and normal samples in a

microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicants argue (Response, 29 October 2004, page 20 and throughout) that even if a prima facie case of lack of utility has been established, it should be withdrawn on consideration of the totality of the evidence. Applicants provide evidence in the form of a publication by Hanna et al. (attached to the Response of 29 October 2004). Applicants contend that the publication teaches that the HER-2/neu gene is under-expressed in certain cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over- expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed polynucleotides is not in currently available form, the asserted utility is not substantial.

35 USC § 112, first paragraph – Written Description.

Claims 1-6, 8-14 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The reasons for this rejection under 35 U.S.C. § 112, first paragraph, are set forth at pp. 10-12 of the previous Office Action (29 July 2004). Briefly, the Applicants were not in possession of all or a significant number of polypeptides that have 80-99% homology to SEQ ID NO: 94, while retaining the function of SEQ ID NO: 94.

Applicants discuss the legal standards applied when evaluating Written Description, including the requirement that written description depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure (pages 23-24, 29 October 2004). The examiner takes no issue with the discussion of general requirements for evaluating Written Description in this case. However, Applicants have not described or shown possession of all polypeptides 80-99% homologous to SEQ ID NO: 94, *that are functionally equivalent to SEQ ID NO: 94*. Nor have Applicants described a representative number of species that have 80-99% homology to SEQ ID NO: 94, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 94.

As discussed in the previous Office Action (29 July 2004) even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed PRO1328 polypeptides, and therefore, would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and

reference to a potential method of making. The claimed product itself is required. Recitation of the phrase "wherein said isolated polypeptide is more highly expressed in normal lung and melanoma tumor ..." (amended claims, 29 October 2004), is not adequate to describe the PRO1328 polypeptide or the polynucleotides encoding the PRO1328 polypeptide, that have 80-99% homology to the PRO1328 polypeptide, since there was no reduction to practice to support the amended claims. Applicants made no variant polypeptides, and as recited in the current Written Description Guidelines, Applicants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire Later

than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
21 January 2005

JANET ANDRES
PRIMARY EXAMINER